Ketene and Carbenoid Behavior of α-Halo Ester Enolates

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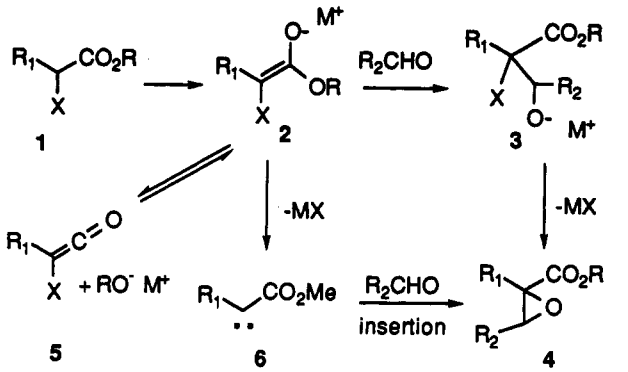
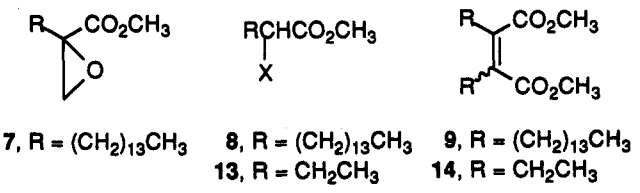
α-Halo esters[2] (1) are important synthons for elaboration of aldehydes and ketones to glycidic esters (Darzens reaction).[3] The mechanism of the Darzens condensation is generally believed to involve an aldol-like condensation between a metalloenolate (2) and carbonyl compound followed by ring closure of the halohydrin intermediate to generate an epoxide (4). In principle, one could also envisage a carbenoid (6) insertion route, which has been ruled out in some studies,[4] or participation of a ketene (5) intermediate[5] (Scheme 1). We report herein evidence to support a ketene–enolate–carbenoid manifold for α-halo ester enolates, a phenomenon which has heretofore gone unnoticed.

We investigated the Darzens condensation of α-halopalmitate and formaldehyde to develop an efficient and high-yielding synthesis of the potential antidiabetic agent, methyl palmoxirate (7), a potent inhibitor of the oxidation of long-chain fatty acids.[6] Use of classical Darzens conditions resulted in low yields of the desired glycidic ester 7. Treatment of methyl α-bromopalmitate (8a) with 1 equiv of sodium hexamethyldisilazide (NaHMDS) at ca. −78 °C in tetrahydrofuran (THF) in the presence of formaldehyde produced none of the desired glycidic ester 7. Surprisingly, the major products found were the cis/trans dimeric olefins 9. Substitution of lithium hexamethyldisilazide (LHMDS) led to a 38% recovery of the glycidic ester 7 and 52% of the dimer mixture 9. Experimentally, we observed quantitative conversion of bromo ester 8a to a nearly 1:1 mixture of dimers 9 using 1 equiv of base.

Scheme 1





7, R = $(CH_2)_{13}CH_3$ 8, R = $(CH_2)_{13}CH_3$ 9, R = $(CH_2)_{13}CH_3$
13, R = CH_2CH_3 14, R = CH_2CH_3
a, X = Br; b, X = Cl

Two reasonable mechanisms for dimeric olefin formation from the α-halo ester enolate of 8a are (1) α-elimination to form a carbenoid species (11) which dimerizes directly or through a carbene addition to the enolate anion (10)[7] followed by elimination of NaBr; and (2) a substitution–elimination reaction of the enolate 10 with starting α-halo ester 8a followed by elimination of HBr[8] (Scheme 2). Similar dimerizations have been observed and attributed to the substitution–elimination mechanism, though these findings usually involve the use of several equivalents of base[9] and/or the intermediacy of a transition metal.[10] Mechanistically, the substitution–elimination pathway requires a minimum of 2 equiv of base: the first for enolate formation and the second for the elimination step (12 to 9). The enolate can serve as a base for the elimination step, so if enolate formation is complete, determination of the number of equivalents of base necessary for the elimination will solve the mechanism question.

We probed the possibility of substitution–elimination reactions through analysis of deuterium quenches. In order to monitor and ensure complete enolate formation,[11] aliquots were withdrawn from the reaction mixture and quenched with 10% acetic acid-d_4/methanol-d_4 and analyzed for deuterium incorporation. When methyl α-bromopalmitate (8a) was allowed to react with LHMDS at −50 °C for 20 min followed by a 10% acetic acid-d_4/methanol-d_4 quench, the major product found was methyl α-bromo-α-deuteriopalmitate (89%) along with minor amounts of 8a (ca. 5%) and methyl-d_3 α-bromo-α-deuteriopalmitate (ca. 6%). The same results were ob-

(1) A.M.Z. was a summer student from Chestnut Hill College working at RWJPRI.

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(4) (a) Zimmerman, H. E.; Ahramjian, L. *J. Am. Chem. Soc.* **1960**, *82*, 5459. (b) Dagli, D. J.; Yu, P.-S.; Wemple, J. *J. Org. Chem.* **1975**, *22*, 3173.

(5) A ketene intermediate was suggested in the self-condensation of a zinc enolate: (a) Vaughan, W. R.; Bernstein, S. C.; Lorber, M. E. *J. Org. Chem.* **1965**, *30*, 1790. Addition of nucleophiles to ketenes has led to enolates: see ref 3d and (b) Tidwell, T. T. *Tetrahedron Lett.* **1979**, 4615. A carbanion mechanism (ElcB) of ester hydrolysis involves ketene intermediates: e.g., (c) Pratt, R. F.; Bruice, T. C. *J. Am. Chem. Soc.* **1970**, *92*, 5956. (d) Remers, W. A.; Roth, R. H.; Weiss, M. J. *J. Org. Chem.* **1965**, 30, 2910. (e) Rebek, J.; Brown, D.; Zimmerman, S. *J. Am. Chem. Soc.* **1975**, *97*, 4407.

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(7) Carbene additions to carbanions are known: (a) Krapcho, A. P.; Huyffer, P. S.; Starer, I. *J. Org. Chem.* **1962**, *27*, 3096. (b) Closs, G. L. *J. Am. Chem. Soc.* **1962**, *84*, 809.

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(10) Hagiwara, H.; Sugioka, T.; Uda, H. *Synth. Commun.* **1984**, *14*, 1193.

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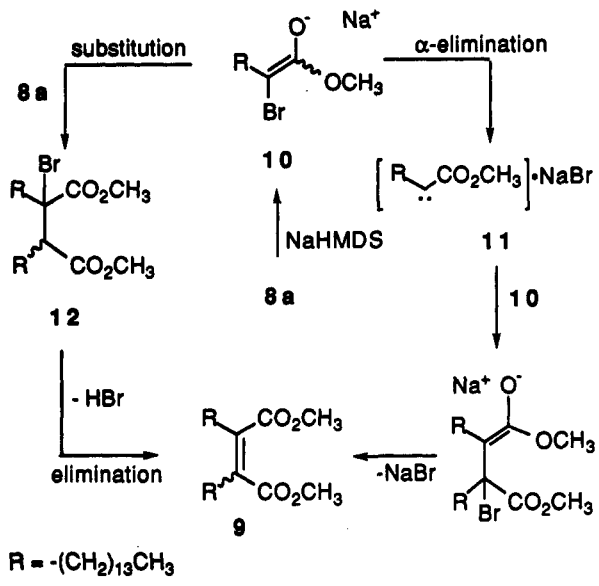
Scheme 2



tained whether the enolate was prepared with 1.0 or 1.5 equiv of lithium diisopropylamide. Incorporation of four deuterium atoms suggests a ketene intermediate, which is trapped by acid-catalyzed addition of methanol-d_4. When these reaction mixtures were allowed to warm slowly to room temperature, the enolates dimerized to a mixture (ca. 1:1) of cis/trans olefins **9**. However, under the same conditions and time scale (20 min at −50 °C), but changing the counterion of the base from lithium to sodium, the reaction of **8a** with NaHMDS led not only to the methyl α-bromo-α-deuteriopalmitate quench product but also to ca. 25% of the dimeric products **9**. Under analogous conditions, the reaction of methyl α-chloropalmitate (**8b**) with lithium or sodium hexamethyldisilazide gave methyl α-chloro-α-deuteriopalmitate as the major product.

The deuterium quenching experiments implicate a nearly quantitative enolate formation and an equilibrium between an α-halopalmitate enolate and an α-halo ketene (**5**)[5,12] at low temperature. The quantitative enolate formation makes the substitution–elimination mechanism highly improbable. The enolate–ketene equilibrium has been previously observed by Schultz and Berger[3] and successfully utilized to prepare glycidic esters by a refined modification to the classic Darzens condensation.

The enolate stability with respect to dimer formation was studied, after establishing that a substitution–elimination mechanism was not operating. We examined the rate of dimerization of the sodium and lithium enolates of methyl α-bromopalmitate (**8a**) and methyl α-chloropalmitate (**8b**). In our rate experiments, the α-halo ester was slowly added to a THF solution (0.1 M) containing

Table 1. Enolate Stability[a]

$$\alpha\text{-halo ester} \xrightarrow{\text{base}} \text{enolate} \xrightarrow{t_{1/2}} \text{olefin/decomposition}$$

entry	α-halo ester	base	temp (°C)[b]	first $t_{1/2}$
1	**8a**	NaHMDS	−50	2 min
2	**8a**	LHMDS	−20	2 h
3	**8b**	NaHMDS	0	7 h[c]
4	**8b**	LHMDS	0	N[d]
5	**13a**	NaHMDS	−50[e]	30 min
6	**13a**	LHMDS	−20	1 h
7	**13b**	NaHMDS	0	1.5 h[c]
8	**13b**	LHMDS	0	N[d]

[a] All reactions carried out in THF at 0.1 M; enolates prepared at −50 °C, unless otherwise noted. [b] Temperature at which dimerization/decomposition was monitored. [c] Decomposition observed. [d] No dimerization observed; only minor decomposition. [e] Enolate prepared at −70 °C.

either LHMDS or NaHMDS and an internal standard (biphenyl) at −50 ± 5 °C . Aliquots were removed at appropriate intervals via precooled syringes, quenched into 10% acetic acid/methanol, and analyzed by GLC for remaining ester. The results are summarized in Table 1. As seen previously, the sodium enolate of methyl α-bromopalmitate (**8a**) was found to dimerize in <10 min at −50 °C. The α-chloro enolates (via **8b**) were more stable at −50 °C and required elevated temperatures to react, thus making a kinetic comparison problematic. Though the true kinetics could not be determined, we were able to determine the first half-life and thus establish several qualitative trends. The lithium enolates are more stable than their sodium counterparts (entry 1 vs 2). The sodium enolate of methyl α-chloropalmitate (entry 3) yielded only a trace of olefinic dimers and eventually decomposed after prolonged reaction time whereas the lithium enolate (entry 4) was found to be stable (minor decomposition observed) at 0 °C for over 8 h. The dimeric products (**9**) are always alkene mixtures (identification by ^{13}C- and ^{1}H-NMR, IR, MS). No halo-substituted dimer contaminants were noted by GC/MS or ^{13}C-NMR.[13]

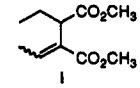
The dimerization phenomenon is not only limited to the long chain α-halo esters. When methyl α-bromo (**13a**) and α-chlorobutyrate (**13b**) were treated with LHMDS or NaHMDS, the enolates formed tended to dimerize to a mixture of cis/trans olefins **14**. The same trends found with the palmitate esters were also observed with the butyrate esters (entries 5–8).[14] The trend for dimerization of the metallo-α-halopalmitic enolates parallels the expected ease for α-elimination to yield carbenes.[15] Attempts to trap a carbene species by generation of the α-bromopalmitate and α-bromobutyrate enolate in the presence of 2,3-dimethylbutene resulted in only trace amounts of the expected cyclopropane derivative[16] as detected by GC-MS. The inability to trap more than a trace of a carbene

(11) Experiments were carried out under strictly anhydrous conditions under argon. THF was freshly distilled from sodium/benzophenone ketyl. The lithium or sodium hexamethyldisilazide (6.1 mL of 1.0 M THF solution) was added using a dry syringe to THF (55 mL). The stirring solution was cooled to the appropriate temperature (−55 °C to −78 °C) using a dry ice/acetone bath. A mixture of α-halo ester (5.5 mmol) and dry biphenyl (400 mg, internal GC standard) in THF (1.0 mL) was added dropwise. At specific time intervals, aliquots (0.75 mL) were withdrawn via a precooled syringe and quickly quenched into 10% acetic acid-d_4/methanol-d_4 solution (3 mL) at −78 °C. The quenched samples were analyzed by GC [30 m × 0.25 mm × 0.25 mm DB-17; 70 °C (2 min) to 300 °C (10 min) @ 20 °C/min] for deuterium content. For the rate studies, the withdrawn aliquots were quenched into 10% acetic acid–methanol solution at −78 °C and analyzed by GC.

(12) Reviews on halogenated ketenes include (a) Brady, W. T. *Synthesis* 1971, 415. (b) Brady, W. T. *Tetrahedron* 1981, *37*, 2949.

(13) To ensure that halogenated dimers could be detected by our analytical techniques, HBr was photolytically added to the alkene mixture; mass spectral analysis indicated formation of a brominated alkyl dimer.

(14) When an excess of base was employed in forming the enolate, the isomeric dimers **1** were detected in the reaction mixtures by GC/MS and ^{1}H NMR.



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(15) (a) Kirmse, W. *Angew. Chem., Int. Ed.*, **1965**, *4*, 1. (b) Kirmse, W. *Carbene Chemistry*; Academic Press: New York, 1971. (c) Hine, J. *Physical Organic Chemistry*; McGraw Hill: New York, 1962.

(16) Similar results were obtained using cyclohexene and 3,4-dihydro-2*H*-pyran as the carbene trap.

species and the facile dimerization to olefins may reflect the aggregation[17] of the enolate or metallocarbenoid derived therefrom. In the palmitate case, self-solvation[18] of the long alkyl chain may also promote the condensation. Alternatively, one might expect that trapping of a carbene with an olefin in the presence of an electron-rich olefin (the enolate) seems highly unlikely.[7]

Consideration of the enolate anion stabilities led to development of a high yielding and practical synthesis of the target compound, methyl palmoxirate (7). Lithium methoxide was substituted for LHMDS, and DMF for THF for environmental and cost considerations. Thus, reaction of methyl "α-lithio-α-chloropalmitate" with paraformaldehyde at room temperature resulted in a high yield of high purity glycidic ester.[19]

In conclusion, enolate stabilities should be carefully appraised when considering the Darzens condensation or any aldol-type reaction dealing with α-halo esters. The realization that a ketene–enolate–carbenoid manifold exists for α-halo ester enolate should lead to improved protocols for organic synthesis. As a result of this investigation, we suggest that the stability of any α-halo ester enolate is a key variable if the glycidic ester is the desired product. Thus, sodium enolates of α-bromo esters decompose faster than they react with formaldehyde, and lithium enolates of α-chloro esters do not decompose at room temperature and react smoothly with formaldehyde to furnish the glycidic esters.

Experimental Section

General Procedures. GLC analyses were performed on a Hewlett-Packard 5890 Series II instrument (FID) and a Hewlett-Packard 3396 Series II integrator using an HP-1 (12 m × 0.2 mm × 0.33 μm) or DB-17 capillary column (30 m × 0.25 mm × 0.25 μm). Biphenyl was used as an internal GLC reference. ^{1}H NMR spectra were recorded using a Bruker AC-300 (300 MHz) instrument in $CDCl_3$ with TMS as internal standard. Melting points are uncorrected. CI (methane) mass spectral data were recorded on a Finnigan 3300 spectrometer and EI (70 eV) data recorded on a VG 7070E instrument. Accurate mass measurements were performed by EI MS using a VG 7070E instrument at 2000 resolution (m/Δm).

First Half-Life Determinations with 8a. General Procedure. LHMDS (6.1 mL of 1.0 M THF solution; 6.1 mmol) was added via a dry syringe to 55 mL of dry THF and cooled with stirring to ca. −50 °C under a nitrogen atmosphere. A mixture of methyl α-bromopalmitate **8a** (1.93 g, 5.52 mmol) and 0.4 g of biphenyl (internal GLC standard) in dry THF (ca. 1 mL) was added dropwise to the stirred solution. The reaction mixture was then warmed to −20 °C. At specific time intervals, aliquots (0.75 mL) were withdrawn using a precooled syringe and quickly quenched by addition to 10% acetic acid/methanol (3 mL) at −78 °C. The samples were analyzed by GLC (see above) to determine the percent of **8a** remaining. The first half-lives were ascertained by graphical analysis.

Dimerization of 8a. Preparation of Mixture 9. Sodium hexamethyldisilazide (30 mL of 1.0 M THF solution; 30 mmol) was added via a dry syringe to dry THF (300 mL) and cooled with stirring to ca. −50 °C under a nitrogen atmosphere. Methyl α-bromopalmitate (**8a**) (10.0 g, 28.7 mmol) in dry THF (30 mL) was added dropwise to the stirred solution. The reaction mixture was then warmed to rt overnight. The reaction mixture was diluted with saturated NH_4Cl and CH_2Cl_2 (500 mL). The organic layer was washed with 1 N HCl and saturated brine and dried with $MgSO_4$, and the solvent was removed in vacuo to yield **9** (7.5 g, 97%) as a wax-like white solid which GLC analysis revealed to be a 1:1 mixture of olefinic dimers. A 200-mg sample was purified by preparative TLC (Uniplate Taper Plate Silica Gel GF) using 5% EtOAc/hexane to afford 90 mg of a less-polar dimer as a white solid: mp 44.0–46.6 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 6.4 Hz, 6H), 1.10–1.36 (m, 48H), 2.26–2.31 (m, 4H), 3.69 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.38, 137.35, 51.70, 31.95, 31.70, 29.72, 29.68, 29.67, 29.60, 29.54, 29.39, 29.34, 28.84, 28.64, 22.71, 14.13; IR ($CHCl_3$) 2927, 2854, 1721, 1463, 1261, 1156, 1127, 1098, 1010 cm^{-1}; accurate mass calcd for $C_{34}H_{64}O_4$ 356.48046, found 356.48045 (Δm = 8.2 ppm). Also recovered was 100 mg of the more-polar dimer as a white solid: mp 41.0–42.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 6.4 Hz, 6H), 1.10–1.36 (m, 48H), 2.30–2.35 (m, 4H), 3.74 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.70, 139.22, 53.35, 33.27, 31.05, 31.03, 31.02, 30.98, 30.88, 30.85, 30.71, 30.69, 29.64, 24.03, 15.44; IR ($CHCl_3$) 2927, 2855, 1718, 1463, 1317, 1271, 1164, 1123, 1095, 1004 cm^{-1}; accurate mass calcd for $C_{34}H_{64}O_4$ 356.48046, found 356.48045 (Δm = 6.3 ppm).

Preparation of Methyl 2-Tetradecylglycidate (7; Methyl Palmoxirate). Methyl α-chloropalmitate (61 g, 0.20 mol) was dissolved in DMF (400 mL) and treated with lithium methoxide (8.35 g, 0.22 mol) with stirring at rt. Solid paraformaldehyde (6.3 g, 0.21 mol) was added portionwise over a period of ca. 8 h and the mixture was stirred overnight. The reaction mixture was diluted with hexane, washed with water several times, and dried with Na_2SO_4, and the solvent was removed in vacuo to afford the title compound (53 g, 89%). Recystallization from methanol yielded **7** as a white crystalline solid, mp 45–48 °C.

(17) For the effect of enolate aggregation on reactivity see (a) Jackman, L. M.; Lange, B. C. *Tetrahedron* 1977, *33* 2737. (b) Jackman, L. M.; Lange, B. C. *J. Am. Chem. Soc.* 1981, *103*, 4494. (c) Jackman, L. M.; Bortiatynski, J. In *Advances in Carbanion Chemistry;* Snieckus, V., Ed.; JAI Press: Greenwich, CT, 1992; Vol. 1, p 45.

(18) Some effects of self-solvation of the long chain and/or aggregation may be used to explain the results obtained by Heathcock in the reactions of aryl esters of α-lithiopalmitate; see Heathcock, C. H.; Pirrung, M. C.; Montgomery, S. H.; Lampe, J. *Tetrahedron* 1981, *37*, 4087.

(19) Process for production of methyl 2-tetradecylglycidate: Maryanoff, C. A. U.S. Patent 4,499,294, 04 Mar 1985.